REMARKS

Applicants note with appreciation the Examiner's entry of the first preliminary amendment filed October 14, 2005, amending claims 1, 15, 24 and 25 and adding new claims 26 and 27, and the second preliminary amendment filed October 24, 2006, amending claims 17 and 18. Applicants also note with appreciation the Examiner's indication that if rewritten in independent form including all of the limitations of claim 1, claims 2-4, 7-10, 13 and 14 would constitute allowable subject matter.

In the Office Action mailed November 17, 2006, the Examiner has restricted the captioned application under 35 U.S.C. §§ 121 and 372 to one of two claim groups: Group I, including claims 1-14, 24 and 25, drawn to compounds of the formula of claim 1, pharmaceutical compositions containing these compounds, and methods of treatment using these compounds; and Group II, including claims 15-23, 26 and 27, drawn to compounds of the formula of claim 15, pharmaceutical compositions containing these compounds, and methods of treatment using these compounds. During a telephone conversation with Applicants' attorney, Kevin L. McLaren, on October 30, 2006, a provisional election was made with traverse to prosecute the invention of Group I, *i.e.*, claims 1-14, 24 and 25; affirmation of the instant election has now been required by the Examiner in this Office Action.

Further, the Examiner has rejected claim 25 under 35 U.S.C. § 112, first paragraph, "as failing to comply with the enablement requirement." Claim 25 is also rejected under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In addition, claims 1, 5, 6, 12, 24, and 25 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Jagtap *et al.* (U.S. Patent No. 6,828,319). Claims 1, 5, 6 and 11 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Lal *et al.* (Indian J Chem 38B:33-39 (1999)). Claims 1, 5 and 6 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Gomes *et al.* (C.R. Acad. Sci., Ser. III 310:1431-1435 (1990)). Finally, claims 2-4, 7-10, 13 and 14 stand objected to as being dependent on a rejected base claim.

Applicants have amended claims 1 and 25, the support for which may be found in the specification. Applicants have added new independent claim 28, which is identical to original dependent claim 8, now canceled, written in independent form including all the limitations of the original base claim 1. As stated above, the Examiner has indicated that this claim is allowable.

Applicants have also added new claims 29-31, which claims depend from new independent claim 28. Applicants have canceled claims 15-23, 26 and 27 drawn to the non-elected Group. Reconsideration of the present application in view of the accompanying amendments to the claims and the reasoning set forth below is respectfully requested.

Restriction Requirement Under 35 U.S.C. §§ 121 and 372

In light of the Examiner's restriction of Applicants' claims under 35 U.S.C. §§ 121 and 372, Applicants hereby affirm the provisional election made with traverse, and elect the invention of Group I, including claims 1-14, 24 and 25, for prosecution in the captioned application. Applicants' cancellation of non-elected claims 15-23, 26, and 27 is done without prejudice to Applicants' right to pursue claims to the invention of the canceled claims in one or more related divisional applications.

Rejection of Claim 25 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claim 25 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement for "contain[ing] subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention." On Pages 4-5 of the Office Action, the Examiner further specifically states that:

> The specification teaches inhibitory effect of instant compounds on topoisomerase I activity as well as cytotoxic effect of instant compounds in vitro using eight different (lung, colon, CNS, ovarian, renal, prostate, breast and melanoma) cell lines as shown in table 1 on page 28. Based on this data, the instant compounds will have utility in treating cancers selected from the group consisting of lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancer. However, *there is no teaching or guidance present in the specification for treating any other disease condition besides treating some cancers. There is no teaching either in the specification or prior art references provided to show that structurally closely related compounds having inhibitory effect on TOP 1 activity are known in the prior art to have therapeutic utility for treating every known disease condition* including every known cancer. There are no working examples present showing efficacy of the instant compound in known animal models of any disease condition. The instant compounds of formula of claim 1 encompasses several hundreds of thousands of compounds based on the values of variables X, Y, Q, R1, RA and RB and therefore, in absence of such teachings, guidance, presence of working examples and the state of the prior art, it would require undue experimentation to demonstrate the efficacy of instant compound

> in known animal models of every known disease condition including cancer cell lines of all known cancers and hence their utility for treating these disease conditions.
>
> (emphasis added)

Applicants agree with the Examiner that "[t]here is no teaching either in the specification or prior art references provided to show that structurally closely related compounds having inhibitory effect on TOP 1 activity are known in the prior art to have therapeutic utility for treating *every known disease condition*..." (emphasis added). Applicants respectfully disagree, however, with the Examiner's contention that "[t]here is no teaching or guidance present in the specification for treating any other disease condition besides treating *some cancers*[ ]" (emphasis added). In light thereof, Applicants have deleted the phrase "a disease state including" from claim 25, such that amended claim 25 reads as follows:

> 25. A method for treating a mammal in need of relief from *cancer*, comprising administering to the mammal an effective amount of a compound according to claim 1.
>
> (emphasis added)

Applicants respectfully point out that, as per MPEP § 2164.05(a), "[t]he specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public (emphasis added). See, *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

Applicants further respectfully suggest that the Examiner is not aware of the state of the prior art in this area, and has not fully appreciated the relevant information incorporated by reference on the first page of Applicants' specification. As known to a person of ordinary skill in the art, a topoisomerase inhibitor is a substance that inhibits topoisomerase enzymes, which enzymes are involved in various DNA processes as well as cell growth. Applicants respectfully direct the Examiner's attention to Pommier *et al.* Biochem Biophys Acta 1400, 83-106 (1998), incorporated by reference in Applicants' specification at page 1, which reference describes that topoisomerase I

("top1") plays a role in the processes of DNA replication, transcription, and recombination (*see*, pages 85-90). Thus, Applicants respectfully point out that top1 inhibitors play a role in diseases, such as cancer, for which one or more of the afore-mentioned processes are effected. Further, as indicated in the instant Pommier reference, top1 is an important chemotherapeutic target; and certain top1 inhibitors, like camptothecins, are currently being used to treat various types of cancer. Topoisomerase inhibitors as chemotherapeutic agents are designed to interfere with the action of topoisomerase enzymes (top1 and top2), which enzymes effect DNA structure by catalyzing the breaking and rejoining of the phosphodiester backbone of DNA strands during the normal cell cycle. As noted at page 1 in Applicants' specification, several camptothecin derivatives such as "irinotecan and topotecan are clinically useful anticancer agents," which agents, *i.e.*, top1 inhibitors, are currently used in colon cancer treatments and ovarian cancer treatment, respectively (*see*, Pommier *et al.*, specifically page 91). Thus, Applicants' specification is enabling for top1 inhibitors as being useful for treating cancers.

Applicants further respectfully direct the Examiner's attention to Kohlhagen *et al.* Molecular Pharmacology 54, 50-58 (1998), incorporated by reference in Applicants' specification at page 1, the first line of which reference states that top1 inhibitor camptothecin (CPT) "derivatives have recently been introduced in the clinic and are among the most promising novel anticancer drugs." The instant Kohlhagen reference also includes extensive discussion about the anticancer activity of camptothecin derivatives. Shown therein in Fig. 2 is the cytotoxicity profile of three such compounds in 60 cell lines of the National Cancer Institute Anticancer Drug Screen (NCI ADS). DNA topoisomerases are important targets for cancer chemotherapy, and one recognized method for the discovery of novel top1 inhibitors is provided by the NCI ADS and the COMPARE analysis (*see*, Kohlhagen *et al.*, specifically pages 55-57).

The Examiner has recognized the *in vitro* test data from eight different cell lines provided in Applicants' specification for compounds of claim 1 synthesized by Applicants. The eight cell lines are similar to the cell lines in the NCI ADS, and thus provide the basis for a path from *in vitro* activity to *in vivo* activity, and, eventually, to clinical studies in humans. As such, the eight cell lines provide a first step toward treatment of various cancers. Applicants respectfully suggest that the Examiner is not aware of the predictive nature of this particular area of research. In drug discovery research, and especially in the area of oncology research, the path from *in vitro* activity to *in vivo* activity and treating disease states is well understood. There is ample evidence in

the oncology area to correlate activity *in vitro* with activity in a disease state. Applicants' *in vitro* experiments were conducted using a National Cancer Institute panel of tumor cell lines, under National Cancer Institute standards, and showed that the claimed compounds inhibit *in vitro* growth of a number of human cancer cell lines, including those of lung, colon, CNS, melanoma, ovarian, renal, prostate, and breast cancer. In view of the above-described data, Applicants respectfully submit that a skilled practitioner would reasonably conclude that the claimed compounds would exhibit therapeutic efficacy against a broad range of cancerous tumors.

The enablement of a specification, in terms of the tests performed and dosage regimens required for treating humans, is addressed in *Cross v. Iizuka* (753 F.2d 1040, 1051, 224 U.S.P.Q. 739, 747-748 (Fed. Cir. 1985)), where the court stated:

> Opinions of our predecessor court have recognized the fact that pharmacological testing of animals is a screening procedure for testing new drugs for practical utility....This in vivo testing is but an intermediate link in a screening chain which may eventually lead to the use of the drug as a therapeutic agent in humans. *We perceive no insurmountable difficulty under appropriate circumstances, in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question.* Successful in vitro testing will marshall resources and direct the expenditure of effort to further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility.
>
> (emphasis added)

The Examiner has acknowledged Applicants' demonstration of *in vitro* activity in eight different cell lines for compounds of claim 1 synthesized by Applicants, which test data, quoting the court in *Cross v. Iizuka*, form "the first link in the screening chain." Applicants respectfully point out that it is well known to a person of ordinary skill in the art, and appreciated by the court, that successful *in vitro* results may be used to stimulate activity toward the successive steps of *in vivo* testing and, eventually, human clinical trials. Applicants further respectfully point out that the process of *in vitro* testing, followed by *in vivo* testing, testing in animal models, and then human clinical trials, has been enabled by Applicants' specification by virtue of the "irinotecan" and "topotecan" examples described therein, which topl inhibitors are currently clinically useful as anticancer agents (*i.e.*, in colon cancer treatments and ovarian cancer treatment, respectively; *see*, Pommier *et al.* Biochem Biophys Acta 1400, 83-106 (1998), incorporated by reference in Applicants' specification at page 1).

Applicants' specification discloses that top1 plays a role in the processes of DNA replication, transcription, and recombination, and, moreover, how top1 inhibitors can be of use in disease states, such as cancer, for which one or more of the afore-mentioned processes are affected. Further, Applicants' specification, through information incorporated by reference, describes top1 inhibitors as chemotherapeutic agents effective against a broad range of cancerous tumors, and how screening via the NCI ADS yields drug candidates as the basis for eventual use of a drug as a therapeutic agent against cancer in humans. Thus, Applicants respectfully submit that establishing a practical utility for a compound of claim 1 in a method for treating a mammal in need of relief from cancer has been enabled by Applicants' specification, and, accordingly, that claim 25, as amended, is enabled by the specification.

Accordingly, Applicants believe that the instant rejection of claim 25 for failure to comply with the enablement requirement has been overcome. Therefore, Applicants respectfully request withdrawal of the instant rejection under 35 U.S.C. § 112, first paragraph.

Rejection of Claim 25 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 25 under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter with applicant regards as the invention." On Page 5 of the Office Action, the Examiner further specifically states that "[i]n claim 25, the term -----disease state ---- is vague and indefinite since specific disease conditions are not defined."

In response to the Examiner's rejection of claim 25 under 35 U.S.C. § 112, second paragraph, Applicants have deleted the phrase "a disease state including" from claim 25, such that amended claim 25 reads as follows:

> 25. A method for treating a mammal in need of relief from *cancer*, comprising administering to the mammal an effective amount of a compound according to claim 1.
>
> (emphasis added)

Accordingly, Applicants believe that the instant rejection of claim 25 for being indefinite has been overcome. Therefore, Applicants respectfully request withdrawal of the instant rejection under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1, 5, 6, 12, 24, and 25 Under 35 U.S.C. §102(e)

The Examiner has rejected claims 1, 5, 6, 12, 24, and 25 under 35 U.S.C. § 102(e) as being anticipated by Jagtap *et al.* (U.S. Patent No. 6,828,319). On Page 5 of the Office Action, the specifically states that:

> Jagtap discloses substituted indeno[1,2-c]isoquinoline derivatives, pharmaceutical compositions containing these compounds and methods of treating various disease conditions using these compounds. The compounds of formulae Ia and Ib where variables R5 represents O or S *and variable X represents —CH(OH)(CH2)n or —CH(arylene)(OH)* disclosed by Jagtap anticipate the instant claims when Y represents CHR2R3 in the instant compounds of formula of claim 1.
>
> (emphasis added)

Applicants traverse the instant rejection and respectfully point out that it is well settled that in order for a single reference to anticipate a claim under 35 U.S.C. § 102, that reference must include, either expressly or inherently, each and every element, *i.e.*, limitation, of the claim. *See*, for example, *In re Verdegaal*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants instantly rejected claims 5, 6, 12, 24, and 25 depend directly from instantly rejected claim 1, for which Q is oxygen or sulfur; X is hydrogen and Y is CHR^2R^3, NHR^2, $NHOR^2$, or $NHNR^2R^3$; or X and Y are taken together to form $=CR^2R^3$; $=NR^2$; $=NOR^2$; or $=NNR^2R^3$. In pointing to compounds of formulae Ia and Ib in Jagtap *et al.*, where variable R_5 represents O or S and variable X represents —$CH(OH)(CH_2)_n$— or —CH(arylene)(OH)—, the Examiner has identified compounds for which, using Applicants' nomenclature, Q is oxygen or sulfur; X is hydrogen and *Y would have to be hydroxyl*. As defined by Applicants' claims, Y does not include an hydroxyl group. Therefore, such compounds, which include an hydroxyl group attached directly to the five-membered ring of the parent structure in Jagtap *et al.*, fall outside the scope of Applicants' claims, and therefore are incapable of anticipating Applicants' claims. Therefore, Applicants respectfully request withdrawal of the instant rejection under 35 U.S.C. § 102(e).

Applicants respectfully point out, however, that compounds of formulae Ia and Ib in Jagtap *et al.*, where variable R_5 represents O or S, variable X represents —$CH(NR_{11}R_{12})$— and wherein R_{11} and R_{12} are independently hydrogen or —C_2-C_9 alkyl, anticipate Applicants' instantly rejected claim 1 when, using Applicants' nomenclature, Q is oxygen or sulfur; X is hydrogen and Y is NHR^2 (wherein R^2 is $-(CH_2)_mZ$, m is an integer from 0-6, and Z is C_1-C_6 alkyl). Accordingly,

Applicants have amended claim 1 to delete recitation of Y as NHR^2, thereby preventing further rejection of Applicants' claims under 35 U.S.C. § 102(e) as being anticipated by Jagtap *et al.*.

Rejection of Claims 1, 5, 6 and 11 Under 35 U.S.C. §102(b)

The Examiner has rejected claims 1, 5, 6 and 11 under 35 U.S.C. § 102(b) as being anticipated by Lal *et al.* (Indian J Chem 38B:33-39 (1999)), and has rejected claims 1, 5 and 6 under 35 U.S.C. § 102(b) as being anticipated by Gomes *et al.* (C.R. Acad. Sci., Ser. III 310:1431-1435 (1990)). On Page 6 of the Office Action, the Examiner specifically states that:

> Lal discloses synthesis/derivatization of 11H-indeno[1,2-c]isoquinolines. *The compounds 6a and 6b* (see page 34 as well as RN 225218-16-6 and 225218-17-7) *disclosed by Lal anticipate the instant claims when Q represents O, R1 represents H and Y represents CHR2R3 group* in the instant compounds of formula of claim 1.
>
> (emphasis added)
>
> Gomes discloses preparation of indeno[1,2-c]isoquinolines. *The compounds 12, 13 and 14* (see page 1434 as well as RN 131673-93-3, 131673-91-1 and 131673-92-2) *disclosed by Gomes anticipate the instant claims when Q represents O, R1 represents H or —(CH2)mZ and Y represents CHR2R3 group* in the instant compounds of formula of claim 1.
>
> (emphasis added)

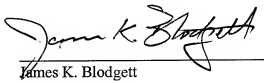
Applicants instantly rejected claims 5, 6, and 11 depend directly from instantly rejected claim 1. In response to the Examiner's rejection of claims 1, 5, 6, and 11 under 35 U.S.C. § 102(b), Applicants have amended claim 1 to delete recitation of Y as CHR^2R^3. Accordingly, Applicants believe that the instant rejection of claims 1, 5, 6, and 11 as being anticipated by Lal *et al.*, and claims 1, 5, and 6 as being anticipated by Gomes *et al.*, each of which reference only disclose compounds having alkyl groups at C-11 of the indenoisoquinoline core structure, has been overcome, and that the instant references likewise do not anticipate any other claim depending from amended claim 1. Therefore, Applicants respectfully request withdrawal of the instant rejections under 35 U.S.C. § 102(b).

CONCLUSION

The foregoing amendments and remarks are believed to be fully responsive to the various rejections raised by the Examiner in the November 17, 2006 Office Action. Applicants believe that this application is in condition for allowance, and respectfully request passage of the application to issuance.

The undersigned would welcome a telephonic interview with the Examiner if the Examiner believes that such an interview would facilitate resolution of any outstanding issues.

Respectfully submitted,
BARNES & THORNBURG LLP



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